Is Metformin Cardioprotective? A New Piece to the Puzzle

Dave L. Dixon, PharmD and Salvatore Carbone, PhD†*

This Commentary relates to the article by D Hu et al on pages 261-269.

Downloaded from http://journals.lww.com/cardiovascularpharm by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC1y0abggQZXdtwnfKZBYtws= on 10/06/2024

Metformin is among the most commonly prescribed medications used primarily to prevent and manage type 2 diabetes mellitus (T2DM) due to its low cost, potent glucose-lowering efficacy, and demonstrated ability to slow the progression of prediabetes to T2DM.[1] Furthermore, it has been proposed that metformin has favorable effects on multiple cardiometabolic risk factors, such as dyslipidemia; however, the mechanisms by which metformin improves dyslipidemia are unclear.[2]

Statins are recommended in all people with diabetes to reduce low-density lipoprotein cholesterol (LDL-C) and atherosclerotic cardiovascular disease risk; however, most of the LDL-C lowering response with statins is achieved at moderate-intensity doses because statins up-regulate the expression of PCSK9, an enzyme responsible for regulating the presence of LDL receptors on the hepatocyte.[3,4] The increased expression of PCSK9 results in greater LDL receptor degradation preventing their recycling to the hepatocyte surface to continue removing LDL-C from the circulation. Furthermore, statins increase the risk of developing T2DM in a dose-dependent manner; however, the benefit of statins outweighs this potential risk.[4] Still, there remains significant interest in mitigating this risk while enhancing the LDL-C lowering effect of statins. Whether the addition of metformin might counteract the negative effects of statins on PCSK9 expression and hyperglycemia has not been previously investigated in a randomized controlled fashion in human subjects.

In this issue of the *Journal*, Hu et al[5] investigated the effects of metformin in patients with coronary heart disease but without diabetes. Specifically, the authors conducted an elegant open-label, placebo-controlled, randomized trial that randomized 80 patients to atorvastatin 20 mg/day, with and without ezetimibe 10 mg/day, or to the same cholesterol-lowering therapy, but with the addition of metformin 850 mg twice per day, for 1 month. Importantly, the group randomized to metformin experienced a greater reduction in LDL-C compared with those who did not receive metformin in addition to cholesterol-lowering therapies. Specifically, adding metformin reduced LDL-C by ~21% compared with only a ~2% reduction in those who did not receive metformin. The reduction in LDL-C was associated with a lower atherosclerotic burden, as reflected by a significantly greater reduction in LDL-particles (LDL-P), especially small dense LDL-P, which is a well-established independent risk factor for cardiovascular disease. In addition to the improvements in LDL-C and LDL-P, metformin use was associated with a greater reduction of serum PCSK9 levels compared with patients randomized to lipid-lowering therapy alone, which may explain the additional LDL-C lowering observed with metformin.

Concerning other cardiometabolic risk factors, although patients treated with lipid-lowering therapy alone experienced a significant increase in fasting glycemia, the addition of metformin prevented this unfavorable metabolic effect. Although this result is not unexpected considering the established glucose-lowering effects of metformin, it provides additional benefits and may perhaps suggest that the addition of metformin to cholesterol-lowering therapies could prevent some of the long-term detrimental effects of statins on

From the *Department of Pharmacotherapy & Outcomes Science, Virginia Commonwealth University School of Pharmacy, Richmond, VA; and †Department of Kinesiology and Health Sciences, Virginia Commonwealth University College of Humanities and Sciences, Richmond, VA.

Dr. D.L. Dixon has received grant funding from Boehringer Ingelheim, Inc. Dr. S. Carbone has nothing to disclose.
The authors report no conflicts of interest.
D.L. Dixon: conceptualization; writing—original draft, review, and editing; S. Carbone: conceptualization; writing—original draft, review, and editing.

Correspondence: Dave L. Dixon, PharmD, Department of Pharmacotherapy & Outcomes Science, Virginia Commonwealth University School of Pharmacy, 410 N. 12th St, Box 980533, Richmond, VA 23298-0533 (e-mail: dldixon@vcu.edu).

Copyright © 2024 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2024 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

SHOUT
SHARE
IT

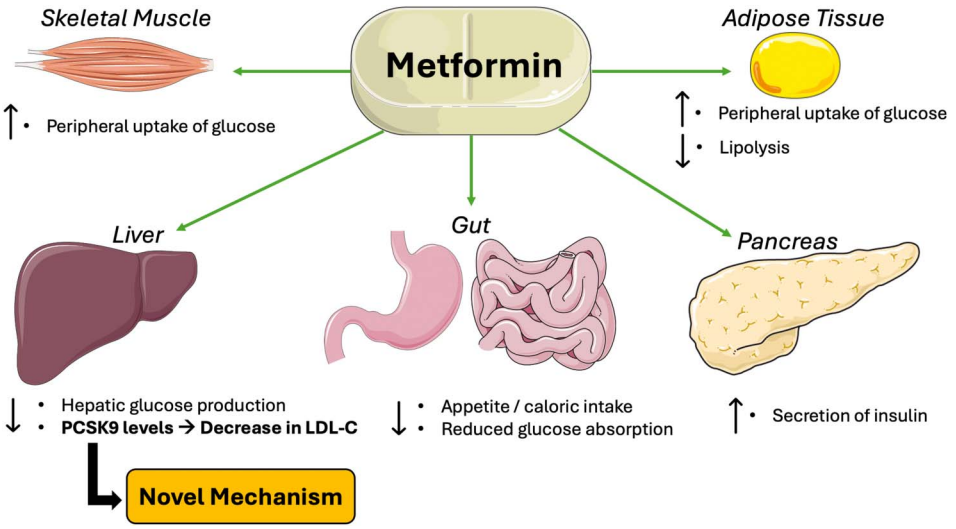

FIGURE 1. Effect of metformin on cardiometabolic risk factors.

glycemic control, even in the absence of T2DM. Notably, metformin reduces the risk of diabetes in individuals with prediabetes, further supporting its use in this population.[6] It is also true that those most likely to progress to T2DM while taking statin therapy are those with risk factors, such as obesity, older age, etc., and therefore should already be on metformin.[6]

The authors are congratulated for providing additional mechanistic data from human subjects that support their previously reported animal data[7] showing the beneficial effects of metformin on lipid and glucose metabolisms. Although metformin has been used for a few decades, its exact mechanisms of action are not fully elucidated. In addition to the herein proposed mechanism of reducing PCSK9 hepatic expression, the benefits of metformin have been attributed to improved insulin resistance, reduced hepatic gluconeogenesis, and increased activation of the adenosine monophosphate-activated protein kinase signaling pathway (Fig. 1).[8]

There are some important notes of caution, however. First, this study was relatively modest in size and prior studies evaluating the effect of metformin on LDL-C levels are conflicting. A meta-analysis of 40 randomized controlled trials and cohort studies with over 1 million participants did not find a significant reduction in LDL-C with metformin.[9] Contrarily, a meta-analysis of 6 randomized controlled trials did find a reduction of ~9 mg/dL with metformin monotherapy.[10] This variability in findings may be due to different patient populations, use of lipid-lowering therapies, study design, and methodological issues, among others. In addition, although LDL-C and LDL-P were reduced, there was only a modest ~7% reduction in apolipoprotein B (apoB), which was not statistically significant. This may be due to discordance or lack of a sufficient sample size to detect a difference in apoB. Finally, the study duration was only 4 weeks, which is the minimum amount of time needed typically to observe notable changes in lipoprotein levels; however, a longer study of 12 weeks would seem like a reasonable next step to confirm these findings.

The benefits of metformin in preventing T2DM in individuals with prediabetes and its improvements in glycemic control in those with established T2DM are well-known and confirmed in relatively large randomized controlled trials. Whether metformin reduces the risk for major adverse cardiovascular events, however, has yet to be studied in a prospective, randomized controlled trial. The ongoing VA-IMPACT trial (NCT02915198) will provide important evidence on whether metformin use reduces the risk for major adverse cardiac events. This trial plans to randomize over 7400 adults with prediabetes and established atherosclerotic cardiovascular disease to metformin (titrated to 2000 mg daily) or placebo. The primary outcome is a composite of death, nonfatal myocardial infarction, stroke, unstable angina, and revascularization.

Overall, the study by Hu and colleagues provides novel insights into the mechanisms of action of metformin. Whether the reported effects might result in improved clinical outcomes has been historically unexplored, with ongoing clinical trials that will help answer this important question. If these effects are confirmed at a large scale, due to its low cost and relatively safe profile, metformin could become an important tool in the hands of providers that can use it not only to reduce T2DM risk in patients with prediabetes or to improve glycemic control in those with established T2DM but also to reduce the risk for cardiovascular events and ultimately survival. Moreover, additional research to further investigate the mechanisms of actions of metformin that might explain these potential beneficial effects is needed.

REFERENCES

1. American Diabetes Association Professional Practice Committee. 9. Pharmacologic approaches to glycemic treatment: standards of care in diabetes-2024 [published correction appears in diabetes care 2024 May 02]. *Diabetes Care*. 2024;47(suppl 1):S158–S178.
2. Li JZ, Li YR. Cardiovascular protection by metformin: latest advances in basic and clinical research. *Cardiology*. 2023;148:374–384.
3. American Diabetes Association Professional Practice Committee. 10. Cardiovascular disease and risk management: standards of care in diabetes-2024. *Diabetes Care*. 2024;47(suppl 1):S179–S218.

Copyright © 2024 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2024 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

Downloaded from http://journals.lww.com/cardiovascularpharm by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC1y0abggQZXdtwnfKZBYtws= on 10/06/2024

4. Taylor BA, Thompson PD. Statins and their effect on PCSK9-impact and clinical relevance. *Curr Atheroscler Rep*. 2016;18:46.
5. Hu D, Qin D, Kuang J, et al. Metformin-induced PCSK9 inhibition further decreases LDL-C following statin treatment in patients with coronary artery disease and without diabetes. *J Cardiovasc Pharmacol.* 2024.
6. American Diabetes Association Professional Practice Committee. 3. Prevention or delay of diabetes and associated comorbidities: standards of care in diabetes-2024. *Diabetes Care*. 2024;47(suppl 1):S43–S51.
7. Hu D, Guo Y, Wu R, et al. New insight into metformin-induced cholesterol-lowering effect crosstalk between glucose and cholesterol homeostasis via ChREBP (Carbohydrate-Responsive element-binding protein)-mediated PCSK9 (proprotein convertase subtilisin/kexin type 9) regulation. *Arterioscler Thromb Vasc Biol*. 2021;41:e208–e223.
8. Foretz M, Guigas B, Viollet B. Metformin: update on mechanisms of action and repurposing potential. *Nat Rev Endocrinol.* 2023;19:460–476.
9. Han Y, Xie H, Liu Y, et al. Effect of metformin on all-cause and cardiovascular mortality in patients with coronary artery diseases: a systematic review and an updated meta-analysis. *Cardiovasc Diabetol.* 2019;18:96.
10. Gillani SW, Ghayedi N, Roosta P, et al. Effect of metformin on lipid profiles of type 2 diabetes mellitus: a meta-analysis of randomized controlled trials. *J Pharm Bioallied Sci.* 2021;13:76–82.

Downloaded from http://journals.lww.com/cardiovascularpharm by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC1y0abggQZXdtwnfKZBYtws= on 10/06/2024

Copyright © 2024 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2024 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.